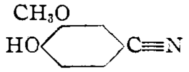
[Contribution from the Institute of Paper Chemistry]

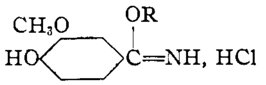
Reactions of Vanillin and its Derived Compounds. XIII.[1] A New Synthesis of Vanillic Acid Esters[2,3]

By Irwin A. Pearl and Donald L. Beyer

Failure to prepare long chain alcohol esters of vanillic acid by direct esterification procedures from vanillic acid led to investigation of the hydrolysis of iminoether hydrochlorides obtained by treating vanillonitrile with long chain alcohols and hydrogen chloride. The long chain alkyl vanillimidate hydrochlorides were easily prepared in good yields. Hydrolysis of these with water alone gave good yields of the normal hydrolysis products, namely, long chain alkyl vanillates and ammonium chloride. Small amounts of the abnormal hydrolysis products, vanillonitrile and long chain alcohol, were also obtained in each case. The long chain alkyl vanillates have the same ultraviolet spectra as other vanillic acid esters and appear useful for the same purposes. Except for the specific activity of the octyl and decyl vanillates toward the spore-forming *Bacillus mycoides*, the long chain alkyl vanillates appear to be very poor antimicrobic agents.

A large number of esters of vanillic acid comprising a variety of types have been prepared recently by several esterification procedures.[4,5] The preparation of a few types of esters, especially those of long chain alcohols, has resisted all direct esterification procedures. Even the use of benzylvanilloyl chloride in accordance with the method employed for higher alcohol esters of gallic acid by Morris and Riemenschneider[6] resulted only in failure. Esterification of vanillonitrile with an alcohol and sulfuric acid did not yield an ester, but vanillonitrile (I) did react in good yield with an alcohol and hydrogen chloride to form an alkyl vanillimidate hydrochloride (II) which in turn yielded the desired ester (III) upon hydrolysis with water alone. This synthesis follows the normal hydrolysis reaction of iminoether hydrochlorides first observed by Pinner[7] and later studied by Stieglitz and co-workers[8] and by Cloke and co-workers,[8] but which apparently has never been employed as a preparative method.


I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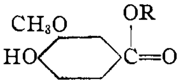
III

The synthesis was first tried for preparation of the well-known ethyl vanillate. Vanillonitrile was prepared by the procedure reported by Ritter[9] and was treated in an excess of absolute ether for five days with a little more than one mole of absolute ethanol and with dry hydrogen chloride. The resulting ethyl vanillimidate hydrochloride was easily filtered and washed. It was dissolved in water and boiled for 30 minutes to give 96% almost pure ethyl vanillate.

In the same manner vanillonitrile was treated with octyl, decyl, dodecyl, tetradecyl, hexadecyl and octadecyl alcohols to form in good yields the corresponding vanillimidic acid ester hydrochlorides. In the case of these long chain alcohols complete reaction took place in two days instead of the five days required for the ethyl ester. The long chain alkyl vanillimidate hydrochlorides were hydrolyzed by boiling with water. These esters, unlike the ethyl ester, were not completely soluble in water. For the most part longer boiling was necessary to bring about complete hydrolysis. Short boiling resulted in recovery of unchanged alkyl vanillimidate and extremely long boiling resulted in some further hydrolysis of the alkyl vanillate to form vanillic acid and the original alcohol. Therefore, care was taken to obtain the optimum time for hydrolysis. In general two hours gave satisfactory results. Under all conditions a small amount of abnormal hydrolysis took place to yield vanillonitrile and the original alcohol. This was most significant in the cases of the decyl and dodecyl vanillimidates. This abnormal hydrolysis of imidoester hydrochlorides by water alone was discussed by Cloke, Knowles and Anderson.[10]

The esters were purified by fractional distillation and were collected, after a little alcohol and vanillonitrile distilled, as colorless oils which solidified to waxy solids, insoluble in water, but very soluble in organic solvents including mineral oil and vegetable oils.

Data for the long chain alkyl vanillimidate hydrochlorides and for the long chain alkyl vanillates are given in Tables I and II, respectively. The ultraviolet absorption spectra of these compounds were determined in purified 95% ethanol with a Beckman spectrophotometer at minimum slit width. The curve for ethyl vanillimidate hydrochloride is reproduced in Fig. 1. Except for the actual specific extinction values, the long chain alkyl vanillimidate hydrochlorides have spectra identical with that of the ethyl ester. In the case of the decyl vanillimidate hydrochloride, exposure to the ultraviolet light in dilute ethanol solution resulted in hydrolysis to the decyl vanillate. Long standing in the same alcoholic solution without exposure to ultraviolet light did not produce hydrolysis. This phenomenon was not experienced with any of the other esters.

The long chain alkyl vanillates possess ultraviolet

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(1) For paper XII of this series, see *J. Org. Chem.*, **16**, 221 (1951).

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(3) This paper represents a portion of the results obtained in the research program sponsored by the Sulphite Pulp Manufacturers' Research League and conducted for the League by The Institute of Paper Chemistry. Acknowledgment is made by the Institute for permission on the part of the League to publish these results.

(4) I. A. Pearl and J. F. McCoy, This Journal, **69**, 3071 (1947).

(5) I. A. Pearl and D. L. Beyer, *ibid.*, **71**, 1066 (1949).

(6) S. G. Morris and R. W. Riemenschneider, *ibid.*, **68**, 500 (1946).

(7) A. Pinner, *Ber.*, **23**, 2943 (1890).

(8) See reference 12 for complete list of papers.

(9) D. M. Ritter, This Journal, **68**, 2738 (1946).

(10) J. B. Cloke, E. C. Knowles and R. J. Anderson, *ibid.*, **58**, 2547 (1936).

TABLE I

LONG CHAIN ALKYL VANILLIMIDATE HYDROCHLORIDES

				Analyses, %					
				Carbon		Hydrogen		Nitrogen	
Alkyl group	Yield, %	M.p.,[a] °C.	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found
Octyl	71	149	$C_{16}H_{26}O_3NCl$	60.84	60.67	8.30	8.06	4.43	4.71
Decyl	94	149–150	$C_{18}H_{30}O_3NCl$	62.86	62.87	8.79	8.75	4.07	4.13
Dodecyl	87	144	$C_{20}H_{34}O_3NCl$	64.58	64.46	9.21	9.14	3.76	3.89
Tetradecyl	87	147–148	$C_{22}H_{38}O_3NCl$	66.06	65.91	9.57	9.47	3.50	3.54
Hexadecyl	67	142–143	$C_{24}H_{42}O_3NCl$	67.34	67.14	9.89	9.81	3.27	3.31
Octadecyl	79	139–140	$C_{26}H_{46}O_3NCl$	68.46	68.30	10.17	10.10	3.07	3.17

[a] All compounds were recrystallized by dissolving in hot chloroform, filtering, cooling, and diluting with anhydrous ether.

TABLE II

LONG CHAIN ALCOHOL ESTERS OF VANILLIC ACID

					Analyses, %				Ultraviolet absorption[a]	
					Carbon		Hydrogen		Max. λ 2930	Max. λ 2630
Ester	Yield, %	B.p. at 1 mm., °C.	M.p., °C.	Formula	Calcd.	Found	Calcd.	Found	k	k
Octyl	81	172–173	15–17	$C_{16}H_{24}O_4$	68.54	68.78	8.63	8.53	24.8	44.0
Decyl	76	185–187	22–26	$C_{18}H_{28}O_4$	70.10	69.97	9.15	9.19	22.2	39.4
Dodecyl	65	198–202	30–32	$C_{20}H_{32}O_4$	71.39	71.36	9.59	9.57	20.1	36.0
Tetradecyl	75	205–215	40–41	$C_{22}H_{36}O_4$	72.49	72.73	9.96	10.04	18.3	32.7
Hexadecyl	90	210–215	48–49[b]	$C_{24}H_{40}O_4$	73.43	73.25	10.27	10.27	17.2	30.8
Octadecyl	76	242–247	57[b]	$C_{26}H_{44}O_4$	74.24	74.17	10.54	10.50	16.1	28.5

[a] The wave length (λ) is in ångström units and k is the specific extinction. [b] Recrystallized from petroleum ether (b.p. 65–110°). All other esters were not recrystallized.

absorption spectra identical with that of the parent acid[11] except for actual extinction values. The specific extinctions for principal maxima and minima are given in Table II.

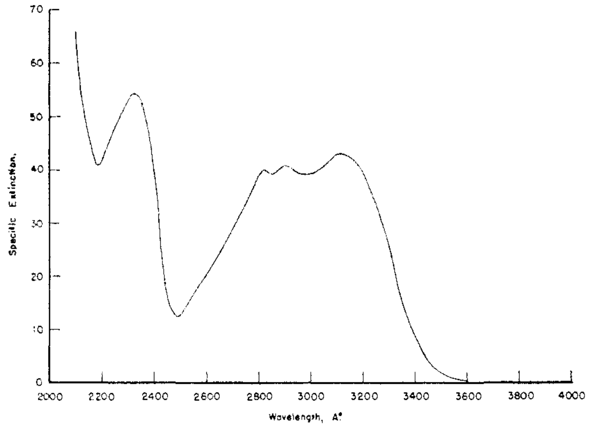

Fig. 1.—Ultraviolet absorption curve for ethyl vanillimidate hydrochloride.

The inhibiting concentrations of these esters were determined for four representative aerobic microorganisms—namely, non-sporeforming (*Aerobacter aerogenes*) and sporeforming (*Bacillus mycoides*) bacteria and two molds (*Aspergillus niger* and *Penicillium expansum*). None of the esters inhibited *Aerobacter aerogenes*, or the two molds at concentrations as high as 0.21%. *Bacillus mycoides* was inhibited by decyl vanillate at 0.009% and by octyl vanillate at 0.003%. Thus the octyl ester is similar in its antibacterial activity to the *n*-hexyl and 2-ethylbutyl vanillates reported earlier.[4]

This method of synthesis suggests itself for the preparation of other difficultly obtainable esters of vanillic acid and related acids, including phenolic and substituted phenolic esters and depsides.

Experimental

All melting points are uncorrected.

Vanillonitrile.—Vanillin oxime was acetylated and dehydrated with acetic anhydride to form acetylvanillonitrile which was partially hydrolyzed with hydrochloric acid according to Ritter.[9]

Ethyl Vanillimidate Hydrochloride.—To a solution of 99 g. of vanillonitrile in 350 cc. of absolute ether was added at room temperature 35 g. of absolute ethanol. The solution was cooled in an ice-bath, saturated with hydrogen chloride gas, and allowed to stand at 20° for 5 days in a flask stoppered with a calcium chloride tube. The crystalline product which separated was filtered, washed with ether, and air-dried. The yield of crude ethyl vanillimidate hydrochloride (melting at 159–160°) was 143 g. (93%). This was purified in over 95% yield by solution in anhydrous methanol and precipitation of the filtered solution with ether to obtain pure ethyl vanillimidate hydrochloride as a colorless crystalline powder melting at 166–167°.

Anal. Calcd. for $C_{10}H_{14}O_3NCl$: C, 51.84; H, 6.09; N, 6.05. Found: C, 51.42; H, 6.07; N, 6.58.

Hartigan and Cloke[12] purified iminoether hydrochlorides by solution in glacial acetic acid and precipitation with anhydrous ether. The alkyl vanillimidate ester hydrochlorides described in Table I were not soluble in anhydrous methanol. Accordingly, they were purified by solution in hot chloroform, filtering, and precipitation with anhydrous ether. All were obtained as colorless powders.

Long Chain Alkyl Vanillimidate Hydrochlorides.—The alkyl vanillimidate hydrochlorides listed in Table I were prepared in a similar manner. However, in all cases the products were filtered after standing at 20° for only 2 or 3 days. Longer standing did not increase yields. Yields reported are for the purified products.

Ethyl Vanillate.—A mixture of 20 g. of ethyl vanillimidate hydrochloride and 250 cc. of water was boiled under reflux for 30 minutes. The clear solution deposited an oil after a few minutes of boiling. The mixture was cooled and extracted with ether. Upon drying and distilling to dryness, the ether yielded a light colored oil which crystallized when seeded with a crystal of ethyl vanillate. The yield was 16.4 g. (96%). Recrystallization from petroleum ether gave white platelets melting at 43–44°. The recrystallization yield was 98%, indicating a crude product of very high purity.

Long Chain Alkyl Vanillates.—The long chain alkyl vanillimidate hydrochlorides were hydrolyzed with water in the same manner. Hydrolysis times of approximately 2 hours were required for maximum yields. The ether extracts of

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(11) I. A. Pearl, THIS JOURNAL, **71**, 2331 (1949).

(12) R. H. Hartigan and J. B. Cloke, *ibid.*, **67**, 709 (1945).

the hydrolysis mixtures were dried and distilled to dryness. The residues were fractionally distilled under reduced pressure to remove some vanillonitrile and long chain alcohol and to recover the desired esters as colorless oils which solidified to low melting solids. Data are given in Table II.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

4-α-Isomaltopyranosyl-D-glucose

BY M. L. WOLFROM, A. THOMPSON[1] AND T. T. GALKOWSKI[1]

The crystalline trisaccharide of D-glucose, herein designated panose, obtained by Pan, Kolachov and associates through the action on maltose of cultures of the mold *Aspergillus niger* NRRL 337, has been reduced to the amorphous glycitol (panitol), characterized as a crystalline dodecaacetate. The acetylated partial hydrolyzate of this glycitol has been chromatographically separated into the following components, all of which have been adequately identified as crystalline substances: panitol dodecaacetate, sorbitol hexaacetate, β-D-glucopyranose pentaacetate, β-isomaltose octaacetate and maltitol nonaacetate. This definitively establishes the structure I (4-α-isomaltopyranosyl-D-glucose) for panose. Calculations have been made for the rate of production of the hydrolytic products of such a trisaccharide alcohol.

The discovery of 4-α-isomaltopyranosyl-D-glucose, a possible hydrolytic product of amylopectin, is an event of major interest in the study of the chemical structure of starch. The synthesis of this new trisaccharide by the action on maltose of an apparent enzyme system contained in the culture filtrate of *Aspergillus niger* NRRL 337 has been reported by Pan, Kolachov and co-workers,[2,3] who demonstrated that the crystalline trisaccharide was composed of D-glucose units. French[4] has proposed for the sugar the structure 4-[6-(α-D-glucopyranosyl)-α-D-glucopyranosyl]-D-glucose or 4-α-isomaltopyranosyl-D-glucose. The sugar and its aldonic acid were partially hydrolyzed by this worker and paper chromatographic evidence was presented for the presence of isomaltose, maltose and D-glucose in the hydrolyzate of the former and of isomaltose (no maltose) and D-glucose in the latter. Further evidence for the presence of one 6-α and one 4-α link was based on the relative positions of the spots from maltotriose, the unknown trisaccharide and a possible trisaccharide from the α-1,6-dextran series. While an excellent exploratory method, paper chromatography does not identify a substance beyond doubt.

We wish to report herein a definitive proof for the structure of this new trisaccharide based upon the isolation and identification of crystalline substances. The sugar was reduced to the corresponding alcohol, thus marking the D-glucose unit possessing the reducing group. The amorphous trisaccharide alcohol was purified through its crystalline dodecaacetate (m.p. 148–150°, $[\alpha]^{27}\text{D}$ +120° in chloroform). The trisaccharide alcohol was then partially hydrolyzed to produce mono- and disaccharide sugars and alcohols. The acetylated hydrolyzate was separated into its five components by silicate chromatography[5] and each was adequately identified as a crystalline substance.

There are three possible trisaccharides of D-glucose joined by one 6-α and one 4-α glycosidic linkage. Reduction of these substances to the glycitols with subsequent partial hydrolysis would produce D-glucose, sorbitol (D-glucitol) and unchanged material from all. In addition, one structure would yield maltitol and isomaltose; a second, maltose and isomaltitol; and a third, maltitol and isomaltitol.

Assuming the structure cited first above, it is desirable to calculate the degree of hydrolysis at which the optimum yield of disaccharide materials would be produced. Herein the assumption is made that the two types of linkages, 6-α and 4-α, would each hydrolyze at their constant rate regardless of location in the disaccharide or trisaccharide cleavage fragment and regardless of the state of reduction of the fragment. The first order specific reaction constants for the 6-α and 4-α unions have been determined[6] in isomaltose and maltose and found to be $k_1 = 0.0208$ and $k_2 = 0.0846$ (hr.$^{-1}$, log$_e$), respectively, when the hydrolysis is carried out in 2% concentration in 0.05 *N* sulfuric acid at 100°. Such a hydrolytic reaction can be expressed by the equation $C = C_0e^{-kt}$ in which C_0 and C are the concentrations of the material at initial time and after time t, respectively. If the initial quantity of material is taken as one mole, the equation reduces to $C = e^{-kt}$. The total amount of material (either disaccharide or trisaccharide units) in moles containing 6-α links at time t could then be represented by

$$C' = e^{-k_1t} \qquad (1)$$

and the amount containing 4-α links would be

$$C'' = e^{-k_2t} \qquad (2)$$

Then $(1 - e^{-k_1t})$ equals the number of moles of material, whether di- or trisaccharide, in which 6-α links have been destroyed and likewise $(1 - e^{-k_2t})$ equals the number of moles in which 4-α links have been destroyed. It follows then that the number of moles of starting material in which both links are broken is

$$(1 - e^{-k_1t})(1 - e^{-k_2t})$$

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(1) Corn Industries Research Foundation Associate (A. T.) and Fellow (T. T. G.) of The Ohio State University Research Foundation (Project 203).

(2) S. C. Pan, A. A. Andreasen and P. Kolachov, *Science*, **112**, 115 (1950).

(3) S. C. Pan, L. W. Nicholson and P. Kolachov, *Abstracts Papers Am. Chem. Soc.*, **118**, 113A (1950); THIS JOURNAL, **73**, 2547 (1951).

(4) D. French, *Science*, **113**, 352 (1951).

(5) W. H. McNeely, W. W. Binkley and M. L. Wolfrom, THIS JOURNAL, **67**, 527 (1945).

(6) M. L. Wolfrom, E. N. Lassettre and A. N. O'Neill, *ibid.*, **73**, 595 (1951).